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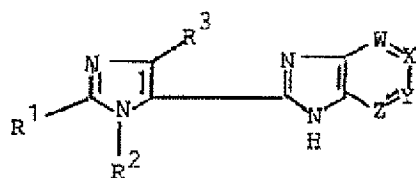
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(71) Applicant:
Merck Patent GmbH, 64293 Darmstadt, DE

(72) Inventor:
Mederski, Werner, Dr., 6106 Erzhausen, DE;
Dorsch, Dieter, Dr., 6105 Ober-Ramstadt, DE;
Oßwald, Mathias, Dr., 6144 Zwingenberg, DE;
Schelling, Pierre, Prof. Dr., 6109 Mühlthal, DE;
Beier, Norbert, Dr., 6107 Reinheim, DE; Lues,
Ingeborg, Dr., 6100 Darmstadt, DE; Minck,
Kaus-Otto, Dr., 6105 Ober-Ramstadt, DE

(54) Imidazole derivatives

(57) Novel imidazole derivatives of formula I



I

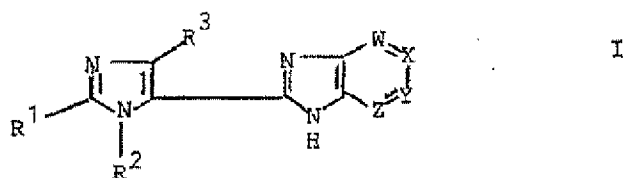
wherein R^1 , R^2 , R^3 and $-W=X=Y=Z-$ have the meaning indicated in patent claim 1, and the salts thereof exhibit angiotensin II-antagonistic characteristics and can be used for the treatment of hypertension, aldosteronism, heart failure and elevated intraocular pressure as well as disorders of the central nervous system.

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The following information was taken from the documents submitted by the applicant
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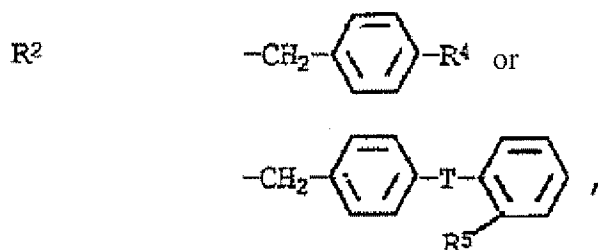
Specification

The invention relates to novel imidazole derivatives of formula I



wherein

$-W=X-Y=Z-$ $-CR^6=CR^7-CR^8=CR^9$, wherein one or two of the groups CR^6 to CR^9 can also be replaced by an N-atom, $-CR^6=CR^7-NR^{10}-CO-$ or $-CO-NR^{10}-CR^8=CR^9-$,
 R^1 refers to A, cycloalkyl with 3-7 C-atoms, OA, SA, alkenyl or alkynyl each with 2-6 C-atoms,



R^3 refers to H, A, Pf or Hal,

R^4 refers to COOR, CN or 1H-5-Tetrazolyl,

R^5 refers to COOR, CN, NO₂, NH₂, NHCOCF₃, NHSO₂CF₃ or 1H-5-Tetrazolyl,

R^6 , R^7 , R^8 and R^9 , independently of each other, refer to H, A, Pf, Hal, OH, OA, COOR, CONH₂, CONHA, CON(A)₂, CN, COA, NO₂, NH₂, NHA, N(A)₂, NHAr, NH-CO-NH₂, NH-CO-NHA, NH-CO-N(A)₂, NH-CO-NH-cycloalkyl with 3-7 C-atoms in the cycloalkyl group, NH-CO-NH-Ar, NH-COOA, NH-COO-alk-Ar, NH-COOAr, NHSO₂A, NH-SO₂Pf, NH-SO₂-Ar, or 1H-5-Tetrazolyl,

R^6 and R^7 (together), R^7 and R^8 (together) or R^8 and R^9 (together) also refer to $-O-CH_2-O-$, R^{10} H, CH₂COOR, CH₂CONH₂, CH₂CONHA, CH₂CON(A)₂, CH₂COA, CH₂COAr, CH₂Ar or CH₂Het,

the R groups, independently of each other, refer to H or A,

T is missing, -NR-CO-, -CO-NR- or -CH=CH-,

A refers to alkyl with 1-6 C-atoms,

Pf refers to perfluoroalkyl with 1-6 C-atoms,

-alk- refers to an alkylene group with 1-4 C-atoms,

Ar refers to an unsubstituted phenyl or naphthyl group or a phenyl or naphthyl group substituted one- or two-fold by A, Pf, Hal, OH, OA, COOR, CN, NO₂, NH₂, NHA and/or N(A)₂,

Het refers to a five- or six-member heteroaromatic group with 1 to 3 N-, O- and/or S-atoms, which can also be condensed with a benzene or pyridine ring, and

Hal refers to F, Cl, Br or I, as well as salts thereof.

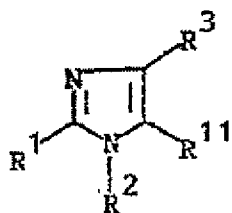
Similar compounds are known from EP-A1-0 253 310.

It was the object of the invention to find novel compounds with valuable characteristics, particularly those which can be used for the manufacture of drugs.

It was discovered that the compounds of formula I and salts thereof possess very valuable pharmacological characteristics with good tolerability. Particularly, they exhibit angiotensin II-antagonistic characteristics and can therefore be used for the treatment of angiotensin II-related hypertension, aldosteronism and heart failure as well as disorders of the central nervous system. These effects can be detected using common in-vitro or in-vivo methods such as those described, for example, in EP-A1-0 468 470, in US Patent 4 880 804 and in WO 91/14367, in addition to A.T. Chiu et al., J. Pharmacol. Exp. Therap. 250, 867-874 (1989), and P.C. Wong et al., *ibid.* 252, 719-725 (1990; in vivo, in rats).

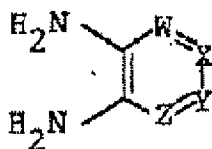
The compounds of formula I can be used as pharmaceutical agents in human and veterinary medicine, particularly for the prophylaxis and/or therapy of cardiac, circulatory and vascular diseases, especially of hypertension and hyperplasia of the blood vessels and of the heart, angina pectoris, heart attacks, strokes, restenoses after angioplasty or bypass operations, arterial sclerosis, elevated intraocular pressure, glaucoma, macular degeneration, hyperuricemia, kidney function disorders, e.g. kidney failure, diabetic nephropathy, diabetic retinopathy, psoriasis, disorders mediated by angiotensin II in female reproductive organs, perception disorders, e.g. dementia, amnesia, memory disorders, conditions of anxiety, depression and/or epilepsy.

The object of the invention are the compounds of formula I, salts thereof as well as a method for the preparation of said compounds and salts thereof, characterized in that one converts a compound of formula II,



II

wherein R^{11} refers to COOH or CHO and R^1 , R^2 and R^3 have the indicated meaning, or one of its reactive derivatives with a compound of formula III,



III

wherein $-W=X=Y=Z-$ has the indicated meaning, with work being performed in the presence of an oxidizing agent in the case $R^{11} = \text{CHO}$, or that a compound of formula I is released from one of its functional derivatives through treatment with a solvolyzing or hydrogenolyzing agent, and/or that, in a compound of formula I, one converts one or more groups R^2 and/or R^3 and/or

$-W=X-Y=Z-$ into one or more other groups R^2 and/or R^3 and/or $-W=X-Y=Z-$ and/or a base or acid of formula I into one of its salts.

In detail, the imidazole derivatives of formula I comprise the following compounds:

Ia 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-benzimidazole
 $(-W=X-Y=Z- = -CR^6=CR^7-CR^8=CR^9-)$;
 Ib 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-1H-imidazo[4,5-b]pyridine
 $(-W=X-Y=Z- = -N=CR^7-CR^8=CR^9-)$;
 Ic 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-3H-imidazo[4,5-b]pyridine
 $(-W=X-Y=Z- = -CR^6=CR^7-CR^8=N-)$;
 Id 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-1H-imidazo[4,5-c]pyridine
 $(-W=X-Y=Z- = -CR^6=N-CR^8=CR^9-)$;
 Ie 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-3H-imidazo[4,5-c]pyridine
 $(-W=X-Y=Z- = -CR^6=CR^7-N=CR^9-)$;
 If 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-1H-imidazo[4,5-c]pyridazine
 $(-W=X-Y=Z- = -N=N-CR^8=CR^9-)$;
 Ig 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-3H-imidazo[4,5-c]pyridazine
 $(-W=X-Y=Z- = -CR^6=CR^7-N=N-)$;;
 Ih 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-imidazo[4,5-d]pyridazine
 $(-W=X-Y=Z- = -CR^6=N=N=CR^9-)$;
 Ii 8-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-9H-purine
 $(-W=X-Y=Z- = -N=CR^7-N=CR^9-)$;
 Ij 8-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-7H-purine
 $(-W=X-Y=Z- = -CR^6=N-CR^8=N-)$;
 Ik 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-imidazo[4,5-b]pyrazine
 $(-W=X-Y=Z- = -N=CR^7-CR^8=N-)$;
 Il 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-4,5-dihydro-4-oxo-3H-imidazo[4,5-c]pyridine
 $(-W=X-Y=Z- = CR^6=CR^7-NR^{10}-CO-)$;
 Im 2-(1- R^2 -2- R^1 -4- R^3 -5-imidazolyl)-4,5-dihydro-4-oxo-1H-imidazo[4,5-c]pyridine
 $(-W=X-Y=Z- = -CO-NR^{10}-CR^8=CR^9-)$.

Here, the respectively tautomeric compounds of formulas Ib and Ic ("imidazo[4,5-b]-pyridine") and those of formulas Id and Ie ("imidazo[4,5-c]pyridine") and those of formulas If and Ig ("imidazo[4,5-c]pyridazine") and those of formulas Ii and Ij ("purine") and those of formulas Il and Im cannot be constitutionally differentiated from each other. The compounds of formula Il and Im can, if $R^{10} = H$, also be present in the form of the tautomeric lactimes $(-W=X-Y=Z- = -CR^6=CR^7-N=C(OH)-$ or $-C(OH)=N-CR^8=CR^9-)$.

In the foregoing and in the following, the groups or parameters $-W=X-Y=Z-$, R^1 to R^{11} , R, T, A, Pf, Ar, Het and Hal have the meanings indicated in formulas I to III unless explicitly indicated otherwise.

In the foregoing formulas, A refers particularly to alkyl with 1-6, preferably 1, 2, 3, or 4 C-atoms, preferably methyl, moreover ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl or tert.-butyl, moreover also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethyl propyl, 1-

ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl.

Accordingly, the R groups are preferably H or alkyl with 1, 2, 3 or 4 C-atoms, particularly methyl or ethyl, the group OA is preferably methoxy, moreover ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy or tert.-butoxy, the group SA is preferably methylthio, moreover ethylthio. The group COOR is preferably COOH, methoxycarbonyl or ethoxycarbonyl, moreover propyloxycarbonyl, isopropyloxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl. The group CONHA is preferably N-methylcarbamoyl or N-ethylcarbamoyl. The group CON(A)₂ is preferably N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl. The group COA is preferably acetyl or propionyl. The group NHA is preferably methylamino or ethylamino. The group N(A)₂ is preferably dimethyl amino or diethyl amino. The group NH-CO-NHA is preferably N'-methyl-ureido or N'-ethyl-ureido. The group NH-CO-N(A)₂ is preferably N',N'-dimethyl-ureido or N',N'-diethyl-ureido. The group NH-COOA is preferably methoxycarbonyl amino or ethoxycarbonyl amino. The group NHSO₂A is preferably methylsulfonyl amino or ethylsulfonyl amino. The group CH₂COOR is preferably carboxymethyl, methoxycarbonylmethyl or ethoxycarbonylmethyl. The group CH₂CONHA is preferably N-methyl-carbamoylmethyl or N-ethylcarbamoylmethyl. The group CH₂CON(A)₂ is preferably N,N-dimethyl-carbamoylmethyl or N,N-diethylcarbamoylmethyl. The group CH₂COA is preferably 2-oxopropyl or 2-oxobutyl.

Cycloalkyl preferably refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, but also 1-, 2-, 3- or 4-methylcyclohexyl, for example.

Accordingly, the group NH-CO-NH-cycloalkyl is preferably N'-cyclopropyl-ureido, N'-cyclobutyl-ureido, N'-cyclopentylureido, N'-cyclohexyl-ureido or N'-cycloheptyl-ureido.

Alkenyl preferably refers to vinyl, 1- or 2-propene-1-yl, 1-propene-2-yl, 1-, 2- or 3-buten-1-yl, 1-, 2- or 3-buten-2-yl.

Alkynyl preferably refers to ethynyl, 1- or 2-propyne-1-yl, 1-, 2- or 3-butine-1-yl.

Pf preferably refers to trifluoromethyl, moreover pentafluorethyl.

Accordingly, the group NH-SO₂Pf preferably refers to trifluoromethylsulfonyl amino.

The group -alk- preferably refers to -CH₂- or -CH₂CH₂-, also preferably -(CH₂)₃- or -(CH₂)₄-, furthermore also -CH(CH₃)-, -CH(CH₃)-CH₂-, -CH₂-CH(CH₃)-, -C(CH₃)₂-.

Hal preferably refers to F, Cl or Br, but also J.

The group Ar is preferably an unsubstituted phenyl group, also preferably a phenyl group monosubstituted in p-position or in o- or m-position as well. Preferred substituents are OA, COOH, COOA and NO₂. Accordingly, Ar is preferably phenyl, o-, m- or (particularly) p-methoxyphenyl, o-, m- or (particularly) p-carboxyphenyl, o-, m- or (particularly) p-

methoxycarbonylphenyl, o-, in- or (particularly) p-ethoxycarbonylphenyl, o-, m- or (particularly) p-nitrophenyl, also preferably o-, m- or (particularly) p-aminophenyl, o-, m- or (particularly) p-dimethylaminophenyl, o-, m- or (particularly) p-diethylaminophenyl, o-, m- or p-tolyl, o-, m- or p-trifluoromethylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m- or p-bromophenyl, o-, m- or p-iodine phenyl, o-, m- or p-cyanophenyl, o-, m- or p-methylaminophenyl, but also e.g. 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxyphenyl, 1- or 2-naphthyl.

Accordingly, the group NHAr is preferably anilino, the group NH-CO-NHAr is preferably N'-phenyl-ureido, the group NH-COO-alk-Ar is preferably benzyloxycarbonyl amino, the group NH-COOAr is preferably phenoxycarbonyl amino, the group NH-SO₂-Ar is preferably phenoxysulfonyl amino, the group CH₂Ar is preferably benzyl.

Het is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, also preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 2,1,5-thiadiazol-3- or -4-yl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2-1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-chinolinyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isochinolinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-chinazolinyl, 1H-1-, -2-, -5-, -6- or -7-imidazo[4,5-b]pyridyl, 3H-2-, -3-, -5-, -6- or -7-imidazo[4,5-b]pyridyl, 1H-1-, -2-, -4-, -6- or -7-imidazo[4,5-c]pyridyl, 3H-2-, -3-, -4-, -6- or -7-imidazo[4,5-c]pyridyl.

Included in the term "Het" are also the homologous groups in which the heteroaromatic ring is substituted by one or more, preferably 1 or 2, A-groups, preferably methyl- and/or ethyl groups, e.g. 3-, 4- or 5-methyl-2-furyl, 2-, 4- or 5-methyl-3-furyl, 2,4-dimethyl-3-furyl, 3-, 4- or 5-methyl-2-thienyl, 3-methyl-5-tert.-butyl-2-thienyl, 2-, 4- or 5-methyl-3-thienyl, 2- or 3-methyl-1-pyrrolyl, 1-, 3-, 4- or 5-methyl-2-pyrrolyl, 3, 5-dimethyl-4-ethyl-2-pyrrolyl, 2-, 4- or 5-methyl-1-imidazolyl, 4-methyl-5-pyrazolyl, 4- or 5-methyl-3-isoxazolyl, 3- or 5-methyl-4-isoxazolyl, 3- or 4-methyl-5-isoxazolyl, 3, 4-dimethyl-5-isoxazolyl, 4- or 5-methyl-2-thiazolyl, 4- or 5-ethyl-2-thiazolyl, 2- or 5-methyl-4-thiazolyl, 2- or 4-methyl-5-thiazolyl, 2,4-dimethyl-5-thiazolyl, 3-, 4-, 5- or 6-methyl-2-pyridyl, 2-, 4-, 5- or 6-methyl-3-pyridyl, 2- or 3-methyl-4-pyridyl, 4-methyl-2-pyrimidinyl, 4, 6-dimethyl-2-pyrimidinyl, 2-, 5- or 6-methyl-4-pyrimidinyl, 2, 6-dimethyl-4-pyrimidinyl, 3-, 4-, 5-, 6- or 7-methyl-2-benzofuryl, 2-ethyl-3-benzofuryl, 3-, 4-, 5-, 6- or 7-methyl-2-benzothienyl, 3-ethyl-2-benzothienyl, 1-, 2-, 4-, 5-, 6- or 7-methyl-3-indolyl, 1-methyl-5- or 6-benzimidazolyl, 1-ethyl-5- or 6-benzimidazolyl.

The group T is preferably missing; moreover, T is preferably -NH-CO-, -N(CH₃)-CO-, -CO-NH-, -CO-N(CH₃)- or -CH=CH-.

The group R¹ is preferably A, particularly butyl, also preferably propyl, pentyl or hexyl.

The group R^2 is preferably 2'-cyan-biphenyl-4-methyl, 2'-carboxy-biphenyl-4-methyl or 2'-(1H-5-tetrazolyl)-biphenyl-4-methyl.

The group R^3 is preferably Hal, particularly Cl.

The group R^4 is preferably COOH, also preferably COOCH₃, COOC₂H₅, CN or 1H-5-Tetrazolyl.

The group R^5 is preferably CN or 1H-5-Tetrazolyl, also preferably COOH, COOCH₃ or COOC₂H₅.

The groups R^6 , R^7 , R^8 and R^9 preferably each refer to H. In the event that they do not all refer to H, preferably only one or two of these groups is different from H and then preferably refer to A (preferably methyl or ethyl), CF₃, Hal (preferably F or Cl), OH, OA (preferably methoxy or ethoxy), COOR (preferably COOH, COOCH₃ or COOC₂H₅), NO₂, NH₂, N(A)₂ (preferably dimethyl amino) or NH-CO-NH₂.

The group R^{10} is preferably H, CH₂COOR (preferably CH₂COOH, CH₂COOCH₃ or CH₂COOC₂H₅), CH₂CON(A)₂ (preferably CH₂CON(CH₃)₂), CH₂COA (preferably CH₂CO-tert.-butyl), CH₂Ar (preferably benzyl) or CH₂Het (preferably CH₂-2-thienyl).

The compounds of formula I may possess one or more chiral centers and therefore occur in various optically active or optically inactive forms. Formula I comprises all of these forms.

Accordingly, those compounds of formula I and Ia to Im are particularly the object of the invention in which at least one of the named groups has one of the preferred meanings indicated in the foregoing. Several preferred groups of compounds can be expressed by the following partial formulas In to Id, which correspond to formulas I and Ia to Im and in which the groups (not further identified) which have the meanings indicated in these formulas but in which in In and Ian to Imn, R^1 refers to A; in Io and Iao to Imo, R^2 refers to 2'-cyan-biphenyl-4-methyl or 2'-(1H-5-tetrazolyl)-biphenyl-4-methyl; in Ip and Iap to Imp, R^1 refers to A and R^2 refers to 2'-cyan-biphenyl-4-methyl or 2'-(1H-5-tetrazolyl)-biphenyl-4-methyl.

Moreover, compounds of the formulas Iq, Iaq to Ipq, Ianq to Imnq, Iaoq to Imoq, Iapq to Impq which correspond to the aforementioned formulas but in which R^3 additionally refers to Cl are preferred.

Particularly, compounds of all formulas mentioned in the foregoing are preferred in which, in addition, one or two of the groups R^6 , R^7 , R^8 or R^9 , independently of each other, refer to H, A, CF₃, Hal, OH, OA, COOR, NO₂, NH₂, N(A)₂ or NH-CO-NH₂, with the remainder of these groups referring to H.

What is more, the compounds of formula I as well as the basic materials for the manufacture thereof are manufactured using inherently known methods as described in the literature (e.g., in the standard works such as Houben-Weyl, *Methoden der organischen Chemie* [Methods of

Organic Chemistry], Georg-Thieme-Verlag, Stuttgart; but particularly in EP-A2-0 468 470 and in US Patent 4 880 804), namely under reaction conditions which are known and suitable for the named conversion. It is also possible to use variations which are inherently known but not mentioned here.

The basic materials can, if desired, also be formed in situ, so that they are not isolated from the reaction mixture, but immediately converted further into the compounds of formula I.

The compounds of formula I can preferably be obtained by converting compounds of formula II with compounds of formula III.

In the compounds of formula II, R^{11} preferably refers to CHO.

The conversion of II with III is expediently performed in the presence of an inert solvent, e.g. an amide such as dimethyl formamide (DMF), dimethyl acetamide or phosphoric acid hexamethyl triamide or a sulfoxide such as dimethyl sulfoxide or a nitrohydrocarbon such as nitrobenzene, at temperatures between about 0 and 200°, preferably 80 and 160°.

If aldehydes of formula II ($R^{11} = \text{CHO}$) are used, then it is expedient to work in the presence of an oxidizing agent such as sodium sulfite. Nitrobenzene can serve simultaneously as a solvent and an oxidizing agent.

The basic materials of formulas II and III are either known or can be produced from known precursors in an inherently known manner. For instance, compounds of formula II are accessible by means of reaction of compounds which otherwise correspond to formula II but have an H-atom instead of R^2 , with halogenides of the formulas $R^2\text{-Cl}$ or $R^2\text{-Br}$.

Moreover, a compound of formula I can be released through solvolysis (e.g. hydrolysis) or hydrogenolysis from one of its functional derivatives.

For instance, primary or secondary amines of formula I in which R^6 , R^7 , R^8 and/or R^9 refer to NH_2 , NHA or NQA can be released from protected derivatives corresponding to formula I but in which NHQ- , NAQ or NQAr groups stand in place of these groups (Q = amino-protecting group such as tert.-butoxycarbonyl or benzyloxycarbonyl) through hydrolysis, e.g. with hydrochloric acid or trifluoroacetic acid or through hydrogenolysis, e.g. on Pd coal at pressures between 1 and 200 bar and at temperatures between 0 and 100° in an inert solvent. Moreover, carboxylic acids of formula I in which R^4 , R^6 , R^7 , R^8 and/or R^9 refer to COOH can be obtained through the hydrogenolysis of appropriate benzyl esters.

Moreover, it is possible to manufacture a compound according to one of the indicated methods which corresponds to formula I but which contains a functionally modified 1H- (or 2H)-5-tetrazolyl group (protected by a protecting group) in place of a 5-tetrazolyl group in the 1-position and split this protecting group off at the conclusion. Suitable examples of protecting groups are triphenylmethyl, which can be split off with HCl or formic acid in an inert solvent or solvent mixture, e.g. ether/dichloromethane/methanol; 2-cyanethyl, which can be split off with

NaOH in water/THF; p-nitrobenzyl, which can be split off with H₂/Raney nickel in ethanol (cf. EP-A2-0 291 969).

The basic substances for the solvolysis or hydrogenolysis can be prepared using inherently known methods, e.g. analogously to the preparation of I from II and III, with appropriate functionally modified basic substances being used.

It is further possible to convert a compound of formula I into another compound of formula I by converting one or more of the groups R² and/or R³ and/or -W=X-Y-Z- into other groups R² and/or R³ and/or -W=X-Y-Z-, for example by reducing nitro groups (for example through hydration on Raney nickel or Pd coal in an inert solvent such as methanol or ethanol) to amino groups and/or functionally modifying free amino and/or hydroxy groups through solvolysis or hydrogenolysis and/or releasing functionally modified amino and/or hydroxy groups and/or releasing functionally modified amino and/or hydroxy groups through solvolysis or hydrogenolysis and/or replacing halogen atoms (e.g. through hydrolysis with hydrochloric acid) with OH groups or (e.g. through reaction with copper(I)cyanide) with CN groups and/or hydrolyzing nitrile groups to COOH groups or to CONH₂ groups or converting with derivatives of hydrozoic acid, e.g. sodium azide in N-methyl pyrrolidone or trimethyltin azide in toluene, to tetrazolyl groups.

For instance, free amino groups can be acylated in the usual manner with an acid chloride or anhydride or free hydroxy and/or NH groups can be alkylated with an unsubstituted or substituted alkyl halogenide or with aldehydes such as formaldehyde in the presence of a reduction agent such as NaBH₄ or formic acid, expediently in an inert solvent such as dichloromethane or tetrahydrofuran (THF) and/or in the presence of a base such as triethylamine or pyridine at temperatures between -60 and +30°.

As desired, a functionally modified amino and/or hydroxy group can be released in a compound of formula I through solvolysis or hydrogenolysis using common methods. For instance, a compound of formula I which contains a COOA group can be converted into the corresponding compound of formula I which contains a COOH group instead. Ester groups can be saponified, for example, with NaOH or KOH in methanol, water, water-THF or water-dioxane at temperatures between 0 and 100°.

In a similar manner, a halogen atom, particularly Cl, can be replaced hydrolytically, e.g. with aqueous HCl solution at temperatures between 20° and boiling temperature, by an OH group. If the halogen atom is in the vicinity of a ring N-atom (e.g. I, -W=X-Y-Z- = -CH=CH-N=CCl-), then the product is generally obtained in the tautomeric lactam form (I, -W=X-Y-Z- = -CH=CH-NH-CO-).

Conversion of nitriles of formula I (R⁴, R⁵, R⁶, R⁷, R⁸ and/or R⁹ = CN) with derivatives of hydrozoic acid leads to tetrazoles of formula I (R⁴, R⁵, R⁶, R⁷, R⁸ and/or R⁹ = 1H-5-tetrazolyl). Preferably, trialkyltin azides such as trimethyltin azide are used in an inert solvent, e.g. an aromatic hydrocarbon such as toluene at temperatures between 20 and 150°, preferably between 80 and 140°, or sodium azide in N-methyl pyrrolidone at temperatures between about 100 and

200°. Subsequently, the trialkyltin group is split off, either through treatment with hydrochloric acid, e.g. in dioxane, or with alkali, e.g. in ethanol/water, or with formic acid, e.g. in methanol, or through chromatography in a silica gel column, e.g. with ethyl acetate/methanol.

A base of formula I can be converted into the respective acid addition salt, for example through conversion of equivalent quantities of the base and the acid in an inert solvent, e.g. ethanol, and subsequent evaporation. Worthy of consideration for this conversion are particularly acids which produce physiologically safe salts. Accordingly, inorganic acids can be used, e.g. sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, as well as organic acids, particularly aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane or ethane sulfonic acid, ethane disulfonic acid, 2-hydroxyethane sulfonic acid, benzene sulfonic acid, p-toluene sulfonic acid, naphthalene mono- and disulfonic acids, lauryl sulfuric acid. Salts with physiologically safe acids, e.g. picrates, can be used for the isolation and/or clean-up of the compounds of formula I.

On the other hand, compounds of formula I which contain COOH or tetrazolyl groups can be converted with bases (e.g. sodium or potassium hydroxide or carbonate) into the corresponding metal, particularly alkali metal or alkaline earth metals, or into the corresponding ammonium salts. The potassium salts are especially preferred.

The novel compounds of formula I and their physiologically safe salts can be used for the manufacture of pharmaceutical preparations by combining them with at least one vehicle or adjuvant and, if desired, with one or more other agents to create a suitable dosage form. The thus-obtained preparations can be used as drugs in human or veterinary medicine. Worthy of consideration as vehicles are organic or inorganic substances which are suited to enteral (e.g. oral or rectal) or parenteral application or for application in the form of an inhaled spray and do not react with the novel compounds, for example water, plant oils, benzyl alcohols, polyethylene glycols, glycerin triacetate and other fatty acid glycerides, gelatins, soy lecithin, carbohydrates such as lactose or starch, magnesium stearate, talc, cellulose. Tablets, dragées, capsules, syrups, juices or drops are used particularly for oral application; of particular interest are sustained-release tablets and capsules with gastric acid-resistant coatings or capsule shells. Suppositories are used for rectal application, solutions, preferably oily or aqueous solutions as well as suspensions, emulsions or implants are used for parenteral application. Sprays which contain the agent either in dissolved or suspended form in a carrier gas or carrier gas mixture (e.g. hydrocarbons such as propane or butane or fluorohydrocarbons such as heptafluoropropane) can be used for application as an inhaled spray. Expediently, the agent is used here in a micronized form, with one or more additional physiologically tolerable solvents being optionally present, e.g. ethanol. Solutions for inhalation can be administered with the aid of common inhalers. The novel compounds can also be used in lyophilized form and the obtained lyophilizates can be used for the manufacture of injection preparations. The cited preparations can be sterilized and/or can contain adjuvants such as preservatives, stabilizing agents and/or wetting agents, emulsifying

agents, salts to influence osmotic pressure, buffers, coloring and/or flavoring agents. If desired, they can also contain one or more other agents, e.g. one or more vitamins, diuretic agents, antiphlogistic agents.

The substances according to the invention are generally administered analogously to other known, commercially available preparations, particularly analogously to the compounds described in US Patent 4 880 804, preferably in doses between about 1 mg and 1 g, particularly between 50 and 500 mg per dose unit.

The daily dose preferably lies between about 0.1 and 100 mg/kg, particularly 1 and 50 mg/kg body weight. The special dose for each particular patient depends, however, on a wide range of factors, for example on the efficacy of the special compound used, on age, body weight, general state of health, sex, nutrition, on the time and mode of administration, the speed of elimination, drug combination and severity of the respective illness for which the treatment is used. Oral application is preferred.

In the foregoing and in the following, all temperatures are indicated in °C. In the following examples, "usual reprocessing" means that water is added if necessary and, depending on the constitution of the final product, the pH is set to values between 2 and 10 if necessary, extraction is performed with ethyl acetate or dichloromethane, separation is performed, the organic phase is dried over sodium sulfate, this is evaporated and purified by means of chromatography on silica gel and/or through crystallization.

Example 1

A mixture of 0.67 g sodium disulfite, 0.98 g 1-(2'-cyanbiphenyl-4-methyl)-2-butyl-4-chloro-5-formyl-imidazole (IIa; F. 102°; can be obtained through oxidation of the corresponding alcohol (EP 0253310, Example 89) with MnO₂) and 45 ml DMF is heated while stirring to 70° and held at 70° for 10 min. 0.32 g 1,2-phenylenediamine is added, boiling is performed for 2.5 h, followed by cooling, lacing with water, filtering of the obtained precipitate, washing again with water, drying, purification by means of chromatography (silica gel; ethyl acetate-hexane 1 : 1), thus obtaining 2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-benzimidazol, F. 157°; Rf 0.33 (ethyl acetate/hexane 1 : 1).

Analogously, from IIa, through conversion with

3-chloro-1,2-phenylene diamine
 4-chloro-1,2-phenylenediamine
 3-chloro-4-ethoxy-1,2-phenylenediamine
 3-methyl-1,2-phenylenediamine
 4-methyl-1,2-phenylenediamine
 4,5-dimethyl-1,2-phenylenediamine
 4-tert.-butyl-1,2-phenylenediamine
 3-nitro-1,2-phenylenediamine
 4-nitro-1,2-phenylenediamine
 3-methoxycarbonyl-1,2-phenylenediamine
 4-methoxycarbonyl-1,2-phenylenediamine

3-ethoxycarbonyl-1,2-phenylenediamine
 4-ethoxycarbonyl-1,2-phenylenediamine
 3-hydroxy-1,2-phenylenediamine
 4-hydroxy-1,2-phenylenediamine
 3-methoxy-1,2-phenylenediamine
 4-methoxy-1,2-phenylenediamine
 3-ethoxy-1,2-phenylenediamine
 4-ethoxy-1,2-phenylenediamine
 3,4-methylenedioxy-1,2-phenylenediamine
 4,5-methylenedioxy-1,2-phenylenediamine
 3-trifluoromethyl-1,2-phenylenediamine
 4-trifluoromethyl-1,2-phenylenediamine
 1,2,3-triaminobenzene 1,2,4-triaminobenzene
 3-dimethyl amino-1,2-phenylenediamine
 4-dimethyl amino-1,2-phenylenediamine

one obtains the following 2-[1-(2'-cyan-biphenyl)-4-methyl]-2-butyl-4-chloro-5-imidazolyl]-benzimidazoles:

4-chloro-
 5-chloro-
 4-chloro-5-ethoxy-
 4-methyl-
 5-methyl-
 5,6-dimethyl-, F. 185°
 5-tert.-butyl- 4-nitro-, F. 186°
 5-nitro-, oil, Rf 0.24 (hexane/ethyl acetate 6 : 4)
 4-methoxycarbonyl-
 5-methoxycarbonyl-, F. 105°
 4-ethoxycarbonyl-
 5-ethoxycarbonyl-
 4-hydroxy-
 5-hydroxy-
 4-methoxy-
 5-methoxy-
 4-ethoxy-
 5-ethoxy-
 4,5-methylenedioxy-
 5,6-methylenedioxy-
 4-trifluoromethyl-
 5-trifluoromethyl-
 4-amino-
 5-amino-
 4-dimethyl amino-
 5-dimethyl amino-.

Example 2

A mixture of 0.3 g IIa, 0.14 g 2-chloro-3,4-diaminopyridine and 10 ml nitrobenzene is stirred for 2 days at 140°. This is followed by evaporation, chromatographing of the residue (ethyl acetate), and one obtains 2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-chloro-3H-imidazo[4,5-c]pyridine, F. 102°.

Analogously, from IIa through conversion with

2,3-diamino pyridine

2,3-diamino-6-methoxy-pyridine

3,4-diamino pyridine

3,4-diamino-5-chloro-pyridazine

2,3-diamino-pyrazine

2,3-diamino-5,6-dimethyl-pyrazine

4,5-diamino-6-hydroxy-pyrimidine

4,5,6-Triamino-pyrimidine

4,5-diamino-pyrimidine

4,5-diamino-6-chloro-pyrimidine

2-chloro-4,5-diamino-pyrimidine

2,4,5-triamino-pyrimidine

2-dimethyl amino-4,5-diamino-pyrimidine

4-dimethyl amino-5,6-diamino-pyrimidine

one obtains the following compounds:

2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-3H-imidazo[4,5-b]pyridine

2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-5-methoxy-3H-imidazo[4,5-b]pyridine

2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-3H-imidazo[4,5-c]pyridine

2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-7-chloro-1H-imidazo[4,5-c]pyridazin

2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-1H-imidazo[4,5-b]pyrazine

2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-5,6-dimethyl-1H-imidazo[4,5-b]pyrazine

8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-hydroxy-9H-purine

8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-amino-9H-purine

8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-9H-purine

8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-chloro-9H-purine

8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-2-chloro-9H-purine

8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-2-amino-9H-purine

8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-2-dimethyl amino-9H-purine

8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-dimethylamino-9H-purine.

Example 3

A mixture of 0.01 mol 1-[2'-(1H-5-tetrazolyl)-biphenyl-4-methyl]-2-butyl-4-chloro-imidazol-5-carboxylic acid (cf. EP 0 253 310, Example 252) and 0.01 mol 1,2-phenylenediamine is added

gradually while stirring to 50 ml POCl_3 . Boil for 4 h, evaporate, reprocess as usual, thus obtaining 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-benzimidazol, F. 240° .

The same compound can be obtained from 1-[2'-(1H-5-tetrazolyl)-biphenyl-4-methyl]-2-butyl-4-chloro-5-formyl-imidazol (cf. EP 0 253 310, Example 132) and 1,2-phenylenediamine analogously to Example 1.

Example 4

A solution of 7.51 g 2-[2'-(1-triphenylmethyl-1H-tetrazolyl)-biphenyl-4-methyl]-2-butyl-4-chloro-5-imidazolyl]-benzimidazol [which can be obtained through reaction of 2-butyl-4-chlorimidazol with 4-bromomethyl-2'-(1-triphenylmethyl-1H-tetrazolyl)-biphenyl to 2-butyl-4-chloro-1-(1-triphenylmethyl-1H-tetrazolyl)-biphenyl-4-methyl-imidazol and conversion with 1,2-phenylenediamine analogously to Example 1] in 30 ml dichloromethane and 30 ml methanol is laced with 20 ml of a solution of HCl in ether and stirred for 3 h at 20° . This is evaporated and reprocessed as, thus obtaining, after chromatographic separation of the triphenylcarbinol formed, 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-benzimidazol; F. 240° .

Example 5

A mixture of 0.37 g 2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-benzimidazol, 0.82 g trimethyltin azide and 20 ml toluene is boiled for 56 h. Evaporation is performed, the residue is taken up in 50 ml methanolic HCl solution, this is stirred for 10 min at 20° , evaporation is performed, this is dissolved again (for drying) in toluene, evaporation is performed and the obtained 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-benzimidazol is chromatographed on silica gel (dichloromethane/methane 9 : 1); Rf 0.80; F. 240° .

Analogously, from the corresponding 2-[1-(2'-cyanbiphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-benzimidazoles, one obtains the following 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-benzimidazols:

4-chloro-
5-chloro-
4-chloro-5-ethoxy-
4-methyl-
5-methyl-
5,6-dimethyl-, F. 232°
5-tert.-butyl-
4-nitro-, F. 142°
5-nitro-, F. 275°
4-methoxycarbonyl-
5-methoxycarbonyl-, F. 171°
4-hydroxy-
5-hydroxy-

4-methoxy-
 5-methoxy-
 4-ethoxy-
 5-ethoxy-
 4,5-methylenedioxy-
 5,6-methylenedioxy-
 4-trifluoromethyl-
 5-trifluoromethyl-
 4-amino-
 5-amino-
 4-dimethyl amino-
 5-dimethyl amino-.

Analogously, one obtains from the corresponding [1-(2'-cyanbiphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl] compounds (cf. Example 2) the following compounds:

2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-3H-imidazo[4,5-b]pyridine
 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-5-methoxy-3H-imidazo[4,5-b]pyridine
 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-3H-imidazo[4,5-c]pyridine
 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-chloro-3H-imidazo[4,5-c]pyridine, F.₂ > 300° (decomposition), R_f 0.06 (ethyl acetate/methanol 9 : 1)
 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-7-chloro-1H-imidazo[4,5-c]pyridazine
 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-1H-imidazol[4,5-b]pyrazine
 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-5,6-dimethyl-1H-imidazo[4,5-b]pyrazine
 8-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-hydroxy-9H-purine
 8-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-amino-9H-purine
 8-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-9H-purine
 8-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-chloro-9H-purine
 8-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-2-chloro-9H-purine
 8-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-2-amino-9H-purine
 8-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-2-dimethylamino-9H-purine
 8-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-dimethylamino-9H-purine.

Example 6

A solution of 1 g 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-5-nitro-benzimidazol in 30 ml ethanol hydrated on 1 g Raney-Ni until absorption of the calculated quantity at 200 and 1 bar. Filtration and evaporation are performed and reprocessing is performed as usual, thus obtaining 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-5-amino-benzimidazol.

Analogously, one obtains 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-amino-benzimidazol from the 4-nitro-isomers.

Example 7

A solution of 2.82 g trifluoromethane sulfonic acid anhydride in 10 ml dichloromethane is added dropwise to a solution of 4.96 g 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-5-amino-benzimidazol and 1.01 g triethylamine in 50 ml dichloromethane at -50 to -60°. This is allowed to heat up to 20°, poured into diluted acetic acid and, after the usual reprocessing, one obtains 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-5-trifluoromethylsulfonyl amino-benzimidazol.

Example 8

A solution of 4.83 g 2-amino-8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-9H-purine and 1.15 g trimethylsilylisocyanate in 40 ml THF is stirred for 1 h at 20°. The solution is concentrated and reprocessed as usual and one obtains 2-ureido-8-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-9H-purine.

Example 9

A solution of 1 g 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-5-methoxycarbonylbenzimidazol, 20 ml 0.1 N aqueous NaOH solution and 35 ml THF is allowed to stand for 48 h at 20°. The THF is evaporated off, acidification is performed with HCl and, after the usual reprocessing, one obtains 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-benzimidazol-5-carboxylic acid.

Analogously, one obtains 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-benzimidazol-4-carboxylic acid from 4-methoxycarbonyl-isomers.

Example 10

A mixture of 1 g 2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-chloro-3H-imidazo [4,5-c]pyridine and 30 ml 15% aqueous HCl is boiled for 4 h, evaporated, reprocessed as usual and one obtains 2-[1-(2'-cyanbiphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4,5-dihydro-4-oxo-3H-imidazo[4,5-c]pyridine, F. 156°. The compound is present in the cited lactam structure and not in the tautomeric lactim structure (-4-hydroxy-3H-imidazo[4,5-c]-pyridine).

Example 11

A solution of 0.01 mol 2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4,5-dihydro-4-oxo-3H-imidazo[4,5-c]pyridine in 40 ml DMF is laced while stirring at 20° with 0.011 mol K-tert.-butylate. After 45 min stirring, a solution of 0.01 mol 2-thienylmethyl chloride is added dropwise to 25 ml DMF. Stirring is performed for another 16 h at 20°, reprocessing is performed as usual, and one obtains 2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4,5-dihydro-4-oxo-5-(2-thienylmethyl)-2H-imidazo[4,5-c]pyridine.

One obtains the following 2-[1-(2'-cyanbiphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4,5-dihydro-4-oxo-5-R¹⁰-3H-imidazo[4,5-c]pyridines analogously:

with bromoacetic acid ester:	-5-ethoxycarbonylmethyl-
with bromoacetamide:	-5-carbamoylmethyl-
with N-Methyl-bromoacetamide:	-5-N-methyl-carbamoylmethyl-
with N,N-dimethyl-bromoacetamide:	-5-N,N-dimethyl-carbamoylmethyl-
with bromo- or chloroacetone:	-5-(2-oxopropyl)-
with 1-bromo-2-butanone:	-5-(2-oxobutyl)-
with 1-bromo-3,3-dimethyl-2-butanone:	-5-(3,3-dimethyl-2-oxobutyl)-
with phenacyl chloride or -bromide:	-5-phenacyl-
with benzyl bromide:	-5-benzyl-
with 2-furylmethyl chloride:	-5-(2-furylmethyl)-
with 5-isoxazolyl-methyl bromide:	-5-(5-isoxazolylmethyl)-.

Example 12

Analogously to Example 5, one obtains from the 2-[1-(2'-cyan-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4,5-dihydro-4-oxo-5-R¹⁰-3H-imidazo[4,5-c]pyridines cited in Example 11 the following 2-[1-(2'-(1H-5-Tetrazolyl)-biphenyl-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4,5-dihydro-4-oxo-5-R¹⁰-3H-imidazo[4,5-c]pyridines:

5-(2-thienylmethyl)-
 5-ethoxycarbonylmethyl-
 5-carbamoylmethyl-
 5-N-methyl-carbamoylmethyl-
 5-N,N-dimethyl-carbamoylmethyl-
 5-(2-oxopropyl)-
 5-(2-oxobutyl)-
 5-(3,3-dimethyl-2-oxobutyl)-
 5-phenacyl-
 5-benzyl-
 5-(2-furylmethyl)-
 5-(5-isoxazolylmethyl)-.

The following examples relate to pharmaceutical preparations which contain the agents of formula I or salts thereof.

Example A: Tablets and dragées

The the usual manner, tablets having the following composition are pressed and coated as needed with a common sucros-based dragée coating:

Agent of formula I	100 mg
Microcrystalline cellulose	278.8 mg
Lactose	110 mg
Corn starch	11 mg
Magnesium stearate	5 mg
Fine silicon dioxide	0.2 mg

Example B: Hard gelatin capsules

Common two-part hard gelatin capsules are each filled with

Agent of formula I	100 mg
Lactose	150 mg
Cellulose	50 mg
Magnesium stearate	6 mg

Example C: Soft gelatin capsules

Common soft gelatin capsules are each filled with a mixture of 50 mg agent and 250 mg olive oil.

Example D: Ampoules

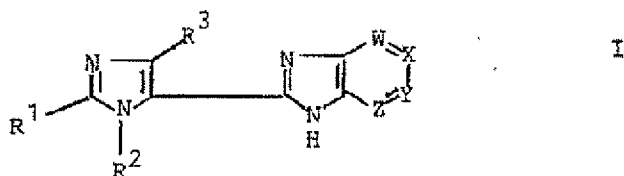
A solution of 200 g agent in 2 kg 1,2-propanediol is filled with water to 10 l and filled in ampoules so that each ampoule contains 20 mg agent.

Example E: Aqueous suspension for oral application

An aqueous suspension is prepared in the usual manner. The unit dose (5 ml) contains 100 mg agent, 100 mg Na-carboxymethyl cellulose, 5 mg Na-benzoate and 100 mg sorbit.

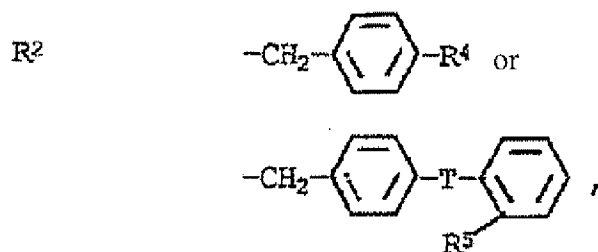
Patent claims

1. Imidazole derivatives of formula I



wherein

$-W=X=Y=Z- -CR^6=CR^7-CR^8=CR^9$, wherein one or two of the groups CR^6 to CR^9 can also be replaced by an N-atom, $-CR^6=CR^7-NR^{10}-CO-$ or $-CO-NR^{10}-CR^8=CR^9-$,
 R^1 refers to A, cycloalkyl with 3-7 C-atoms, OA, SA, alkenyl or alkynyl each with 2-6 C-atoms,



R^3 refers to H, A, Pf or Hal,

R^4 refers to COOR, CN or 1H-5-tetrazolyl,

R^5 refers to COOR, CN, NO₂, NH₂, NHCOCF₃, NHSO₂CF₃ or 1H-5- tetrazolyl,

R^6 , R^7 , R^8 and R^9 , independently of each other, refer to H, A, Pf, Hal, OH, OA, COOR, CONH₂, CONHA, CON(A)₂, CN, COA, NO₂, NH₂, NHA, N(A)₂, NHA, NH-CO-NH₂, NH-CO-NHA, NH-CO-N(A)₂, NH-CO-NH-cycloalkyl with 3-7 C-atoms in the cycloalkyl group, NH-CO- NH-Ar, NH-COOA, NH-COO-alk-Ar, NH-COOAr, NHSO₂A, NH-SO₂Pf, NH-SO₂-Ar, or 1H-5-tetrazolyl,

R^6 and R^7 (together), R^7 and R^8 (together) or R^8 and R^9 (together) also refer to $-O-CH_2-O-$, R^{10} H, CH₂COOR, CH₂CONH₂, CH₂CONHA, CH₂CON (A)₂, CH₂COA, CH₂COAr, CH₂Ar or CH₂Het,

the R groups, independently of each other, refer to H or A,

T is missing, $-NR-CO-$, $-CO-NR-$ or $-CH=CH-$,

A refers to alkyl with 1-6 C-atoms,

Pf refers to perfluoroalkyl with 1-6 C-atoms,

-alk- refers to an alkylene group with 1-4 C-atoms,

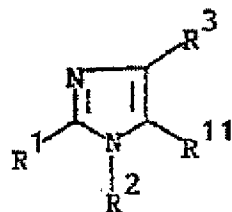
Ar refers to a substituted or a phenyl or naphthyl group substituted one- or two-fold by A, Pf, Hal, OH, OA, COOR, CN, NO₂, NH₂, NHA and/or N(A)₂,

Het refers to a five- or six-member heteroaromatic group with 1 to 3 N-, O- and/or S-atoms, which can also be condensed with a benzene or pyridine ring, and

Hal refers to F, Cl, Br or I, as well as salts thereof.

2. a) 2-[1-(2'-cyan-biphenyl)-4-methyl]-2-butyl-4-chloro-5- imidazolyl]-benzimidazol
- b) 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl)-4-methyl]-2-butyl-4-chloro-5-imidazolyl]-benzimidazol
- c) 2-[1-(2'-cyan-biphenyl)-4-methyl]-2-butyl-4-chloro-5-imidazolyl]-5-nitro-benzimidazol
- d) 2-[1-(2'-(1H-5-tetrazolyl)-biphenyl)-4- methyl)-2-butyl-4-chloro-5-imidazolyl]-5-nitro-benzimidazol
- e) 2-[1-(2'-cyan-biphenyl)-4-methyl)-2-butyl-4-chloro-5-imidazolyl]-4-nitro-benzimidazol.

3. Method for the manufacture of imidazole derivatives of formula I as set forth in claim as well as salts thereof, characterized in that one converts a compound of formula II,



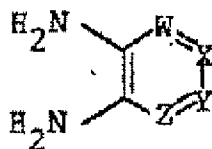
II

wherein

R^{11} refers to COOH or CHO and

R^1 , R^2 and R^3 have the indicated meaning,

or one of its reactive derivatives with a compound of formula III,



III

wherein

$-W=X-Y=Z-$ has the indicated meaning,

with work being performed in the presence of an oxidizing agent in the case $R^{11} = \text{CHO}$,

or that a compound of formula I is released from one of its functional derivatives through

treatment with a solvolyzing or hydrogenolyzing agent, and/or that, in a compound of formula I,

one converts one or more groups R^2 and/or R^3 and/or $-W=X-Y=Z-$ into one or more groups R^2 and/or R^3 and/or $-W=X-Y=Z-$ and/or a base or acid of formula into one of its salts.

4. Method for the manufacture of pharmaceutical preparations, characterized in that a compound of formula I as set forth in claim 1 and/or a physiologically safe salt thereof is combined with at least one solid, liquid or semisolid vehicle or adjuvant to create a suitable dosage form.

5. Pharmaceutical preparation, characterized in that it contains at least one compound of formula I as set forth in claim 1 and/or a physiologically safe salt thereof.

6. Compound of formula I as set forth in claim 1 and physiologically safe salts thereof for combatting illnesses.

7. Use of compounds of formula I as set forth in claim 1 and/or physiologically safe salts thereof for the manufacture of a drug.

8. Use of compounds of formula I as set forth in claim 1 and/or physiologically safe salts thereof in the combatting of illnesses.

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